(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 July 2003 (10.07.2003)

PCT

(10) International Publication Number
WO 03/055902 A1

(51) International Patent Classification[7]: C07K 5/083

(21) International Application Number: PCT/IB02/05583

(22) International Filing Date:
23 December 2002 (23.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0104463-5 29 December 2001 (29.12.2001) SE

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/055902 A1

(54) Title: INTERMEDIATES FOR LHRH ANTAGONIST SYNTHESIS, PROCESS FOR THEIR PRODUCTION, AND PROCESS FOR LHRH ANTAGONIST PRODUCTION

(57) Abstract: The novel tripeptides Ac-D-2Nal-D-4ClPh-D-3Pal-OH and Boc-D-2Nal-D-4ClPhe-D-3Pal-OH are intermediates useful in the synthesis of LHRH analogs by coupling with suitable heptapeptides, in particular with the heptapeptides P^1-Ser(P^2)-NMeTyr(P^3)-D-Lys(Nic)-Leu-Lys(iPr,P^4)-Pro-D-AlaNH$_2$ and P^1-Ser(P^2)-NMeTyr(P^3)-D-Asn-Leu-Lys(iPr,P^4)-Pro-D-AlaNH$_2$.

INTERMEDIATES FOR LHRH ANTAGONIST SYNTHESIS, PROCESS FOR THEIR PRODUCTION, AND PROCESS FOR LHRH ANTAGONIST PRODUCTION

FIELD OF THE INVENTION

The present invention relates to intermediates for the synthesis of LHRH antagonists, to a process for the production of these intermediates and to a process for the production of LHRH antagonists.

BACKGROUND OF THE INVENTION

The luteinizing hormone-releasing hormone, LHRH, controls the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH). LHRH antagonists are compounds capable of blocking the secretion of FSH and LH. They are generally nona- and decapeptides (but may be shorter or longer) comprising part of or the entire structure of LHRH in which one or several amino acids have been exchanged for other natural amino acids and/or amino acids not found in nature.

Synthetic LHRH antagonists may be used for contraception and in the treatment of benign hyperplasia of the prostate gland, hormonal-dependent tumors of the breast and ovaries, dysmenorrhea, endometriosis, and other conditions. These synthetic LHRH antagonists have the general formula

$Ac\text{-}D\text{-}2Nal\text{-}D\text{-}4ClPhe\text{-}D\text{-}3Pal\text{-}Ser\text{-}X\text{-}NH_2$,

wherein X is from 5 to 6 natural and/or synthetic amino acid residues. More particularly they have the aforementioned general formula wherein X is AA1-AA2-Leu-AA3-Pro-D-Ala, in particular wherein AA1 is a natural or synthetic amino acid and AA2 is a natural or synthetic amino acid or zero, AA3 is a natural or synthetic amino acid.

While there are a number of synthetic methods for preparing LHRH analogs known in the art, there is a need for improvement since the total yield of LHRH analogs obtained from known processes is not high and the products, in addition, may require extensive purification. Moreover, the methods for the synthesis of LHRH analogs known in the art are quite costly.

A synthesis strategy disclosed in U.S. patent no. 5,710,246 for making decapeptide or nonapeptide LHRH antagonists comprises the coupling of an intermediate tripeptide representing amino residues 1 to 3 (counting starts at the amino terminal of the peptide) with a heptapeptide or a hexapeptide, respectively representing amino acid residues 4-10 and 4-9, respectively. The intermediate tripeptide disclosed in US 5710246 A is an ester, Boc-D-2Nal-D-4ClPhe-D-3Pal-O-Me or the corresponding benzyl or allyl ester.

OBJECTS OF THE INVENTION

It is thus an object of the invention to provide a tripeptide intermediate for the 3+7 and 3+6 synthesis of LHRH analogs in which the yield and/or purity of the product is improved.

It is another object of the invention to provide a process for the production of such a tripeptide intermediate.

It is still another object of the invention to provide a process for the production of LHRH analogs in which a tripeptide is coupled to a hepta- or hexapeptide.

Further objects of the invention will become obvious from the following summary of the invention, the description of preferred embodiments, and the appended patent claims.

DEFINITIONS AND ABBREVIATIONS

For definitions and abbreviations used in this application and which are generally accepted in the field of the invention reference is made in particular to US 5710246 A.

SUMMARY OF THE INVENTION

According to the invention is provided a tripeptide representing amino acids 1-3 of an LHRH antagonist, the terminal amino group of which is Boc- or Ac-protected and the terminal carboxyl group of which (that is, the terminal group of amino acid no. 3) is not protected.

According to the invention is disclosed the tripeptide (I)

Ac-D-2Nal-D-4ClPhe-D-3Pal-OH (I)

which is a useful intermediate in a process for the synthesis of an LHRH antagonist of the general formula (II)

Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser-X-NH_2 (II)

wherein X is from 5 to 7 natural and/or synthetic amino acid residues, more preferred AA1-AA2-Leu-AA3-Pro-D-Ala, in particular wherein AA1 is a natural or synthetic amino acid and AA2 is a natural or synthetic amino acid or zero, AA3 is a natural or synthetic amino acid.

Still preferred is the use of the tripeptide (I) in the synthesis of a peptide of the general formula (IIa)

Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser-AA1-AA2-Leu-Lys(iPr)-Pro-D-Ala-NH_2 (IIa),

wherein AA1 and AA2 have the meaning given above, in particular a LHRH antagonist of the formula (III)

Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser-MeTyr-D-Lys(Nic)-Leu-Lys(iPr)-Pro-D-Ala-NH_2 (III)

or, even more preferred, of the formula (IIIa)

Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser-MeTyr-D-Asn-Leu-Lys(iPr)-Pro-D-Ala-NH_2 (IIIa).

According to the invention is also disclosed the tripeptide

Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX)

of same utility.

Furthermore, according to the invention is disclosed a process for preparing a tripeptide of the formula (I)

Ac-D-2Nal-D-4ClPhe-D-3Pal-OH (I)

or (IX)

Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX),

comprising the following consecutive steps for the preparation of (I):

(a) Reacting Boc-D-4ClPhe-OH with HONSu to form Boc-D-4ClPhe-OSu (VII);

(b) Reacting Boc-D-4ClPhe-OSu (VII) with H-D-3Pal-OH to form Boc-D-4ClPhe-D-3Pal-OH (VIII);

(c) Reacting Boc-D-4ClPhe-D-3Pal-OH (VIII) with Boc-D-2Nal-OSu prepared by reacting Boc-D-2Nal-OH with HONSu to form Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX);

(d) Reacting Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX) with acetic acid to form Ac-D-2Nal-4ClPhe-D-3Pal-OH (I);

or the consecutive steps (a) through (c) for the preparation of (IX).

The process of the invention for preparing a LHRH antagonist comprises the step of coupling the tripeptide (I) with a heptapeptide (IV) of the general formula

P^1-Ser(P^2)-AA1-AA2-Leu-Lys(iPr,P^4)-Pro-D-AlaNH$_2$ (IV),

wherein P^4 is H or an amino protecting group such as Boc, wherein AA1 and AA2 have the aforementioned meaning, in particular with a heptapeptide (V) of the general formula P^1-Ser(P^2)-NMeTyr(P^3)-D-Lys(Nic)-Leu-Lys(iPr,P^4)-Pro-D-AlaNH$_2$ (V), wherein P^1 is selected from H or amino protecting group and P^2 and P^3 are independently selected from H and -OH protecting group, and P^4 has the meaning given above, for preparing the LHRH antagonist Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser-MeTyr-D-Lys(Nic)-Leu-Lys(iPr)-Pro-D-Ala-NH$_2$ (III),

more particularly with a heptapeptide (Va) of the general formula P^1-Ser(P^2)-NMeTyr(P^3)-D-Asn-Leu-Lys(iPr,P^4)-Pro-D-$AlaNH_2$ (Va), wherein P^1 is selected from H or amino protecting group and P^2 and P^3 are independently selected from H and -OH protecting group, and P^4 has the meaning given above, for preparing the LHRH antagonist Ac-D-2Nal-D-4ClPhe-D-3Pal-Ser-MeTyr-D-Asn-Leu- Lys(iPr)-Pro-D-Ala-NH_2 (III).

The heptapeptide (V) is described in US 5710246 A. The heptapeptide of the general formula (IV) including the heptapeptide (Va) can be synthesized by routine modifications of the synthesis of (V) or by coupling the corresponding Boc-amino acids on a peptide synthesizer (Beckman Model 990), as described in WO 94/40757 where also the LHRH antagonist (III) is disclosed.

Alternatively the process of the invention for preparing a LHRH antagonist comprises the step of coupling the tripeptide (IX)

Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX)

with a heptapeptide (IV) of the general formula

P^1-Ser(P^2)-AA1-AA2-Leu-Lys(iPr,P^4)-Pro-D-$AlaNH_2$ (IV),

wherein P^1, P^2, P^4, AA1 and AA2 have the meaning given above, in particular with a heptapeptide (V) of the general formula

P^1-Ser(P^2)-NMeTyr(P^3)-D-Lys(Nic)-Leu-Lys(iPr,P^4)-Pro-D-$AlaNH_2$ (V)

or, even more preferred, with a heptapeptide of the general formula (Va)

P^1-Ser(P^2)-NMeTyr(P^3)-D-Asn-Leu-Lys(iPr,P^4)-Pro-D-AlaNH_2 (Va),

wherein P^1 is selected from H or amino protecting group, P^2 and P^3 are independently selected from H and -OH protecting group, P^4 has the aforementioned meaning, followed by substituting the N-terminal Boc group by an acyl group, in particular an acetyl group.

More particularly, the heptapeptide of the general formula (V) is the heptapeptide (VI)

H-Ser(tBu)-NMeTyr-D-Lys(Nic)-Leu-Lys(iPr,Boc)-Pro-D-AlaNH_2 (VI),

or even more preferred, the heptapeptide (VIa)

H-Ser(tBu)-NMeTyr-D-Asn-Leu-Lys(iPr,Boc)-Pro-D-AlaNH_2 (VIa).

A particular advantage with the method of the invention is that a cheaper starting material, H-D-Pal-OH·2HCl, can be used instead of the ester H-Pal-OR·2HCl; the protective group of the starting material need not be removed. Therefore the synthesis of the invention is one step shorter and avoids that material is lost in the additional step. Another advantage is that the formation of impurities in the saponification step is avoided. The formation of such impurities is well known. For instance, the basic conditions at the ester hydrolysis step cause partial racemization of D-Pal. The other prior-art alternative of removing the ester group by catalytic hydrogenation (in the case of allyl or benzyl ester groups) risks to cause a loss of Cl from 4ClPhe producing Phe. While allyl groups may be removed by still other reagents the full removal is difficult to control.

The invention will now be explained in more detail by reference to a preferred embodiment.

DESCRIPTION OF A PREFERRED EMBODIMENT OF THE INVENTION

Synthesis of Ac-D-2Nal-4ClPhe-D-3Pal-OH (I).

EXAMPLE 1. Boc-D-4ClPhe-OSu. Boc-D-4ClPhe-OH (299,75 g; 1,0 eq.) and HONSu (184,1 g; 1,6 eq.) are dissolved in 2-propanol (4,5 L). The mixture is cooled to 0°C and DIC (164,1 g; 1.3 eq.) is added. The mixture is stirred for 16h while warming to room temperature. The product is filtered of, washed with 2-propanol (1,5 L) and dried. Yield: 85%. HPLC purity: 98,8%.

EXAMPLE 2. Boc-D-4ClPhe-D-3Pal-OH. H-D-3Pal-OH, 2 HCl (251,1 g; 1,05 eq.) and Boc-D-4ClPhe-OSu (396,8 g; 1,0 eq.) are dissolved in DMSO (3,33 L) and NMM (318,8 g; 3,15 eq.) is added. The mixture is stirred for 16 h at room temperature. Water (17 L) is added and pH is adjusted to 4-4,5 which causes the product to precipitate. The mixture is filtered and the product is washed with water (3 x 5 L) to remove traces of DMSO, H-D-3Pal-OH and Boc-D-4ClPhe-OH. The product is dried. Yield: 80%. HPLC purity: 97,8%

EXAMPLE 3. Boc-D-2Nal-OSu. Boc-D-2Nal-OH (315,4 g; 1,0 eq.) is dissolved in 2-propanol (6,8 L) at -10°C and IBC (157 g; 1,15 eq.) and NMM (116 g; 1,15 eq.) is added. After stirring for 5-10 min a mixture of HONSu (230,1 g; 2,0 eq.) in 2-propanol (1,4 L) is added. Additional NMM (10,1 g; 0,1 eq.) is added. After half an hour water (0,82 L) is added to dissolve precipitated NMM·HCl. The product is isolated by

filtration, washed with 2-propanol (1 L), and dried. Yield: 90%. HPLC purity: 98,3%.

EXAMPLE 4. Boc-D-Nal-D-4ClPhe-D-3Pal-OH.

(a) *Deprotection*. Boc-D-4ClPhe-D-3Pal-OH (447,93 g; 1,0 eq.) is dissolved in a mixture of ethyl acetate (3,4 L), acetic acid (675 ml) and MSA (454 mL; 7,0 eq.) at 0°C and kept at this temperature for two hours. TEA (1669 ml; 12 eq.) is added.

b) *Condensation*. Boc-D-Nal-OSu (412,4 g; 1,0 eq.) is added to the neutralized deprotection mixture at room temperature. The reaction mixture is kept at this temperature for 2-4 h. Aq. 25% NH_3 (154 mL; 2,0 eq.) is added to quench remaining hydroxysuccinimide ester. 1-Butanol (4,5 L) is added to prevent precipitation in the subsequent extractions.

c) *Purification and isolation*. The reaction mixture is extracted twice at pH 6 (2 x 4,5 L water) to remove TEA, at pH 9 (4,5 L water) to remove MSA and finally at pH 7 (4,5 L water). The extractions are carried out at 40-45°C to prevent precipitation. To the organic phase is added acetic acid (4,5 L; 1 vol.) and the mixture is concentrated *in vacuo* and co-evaporated with acetic acid (4,5 L) to give a solid.

EXAMPLE 5. Ac-D-2Nal-D-4ClPhe-D-3Pal-ONa.

a) *Deprotection*. To the solid Boc-D-2Nal-D-4ClPhe-D-3Pal-OH is added water (90 ml), acetic acid (1,8 L) and MSA (454 mL; 7,0 eq.) and the mixture is stirred for 1-2 h at room temperature. The mixture is cooled to 0°C and neutralized with TEA (1071 ml; 7,7 eq.). The solution is concentrated *in vacuo* and co-evaporated twice with toluene (2 x 2,5 L) to give an oil.

b) *Acetylation*. The oil from the deprotection step is dissolve in toluene (2,0 L) and acetyl imidazole (132,14 g) is added.

The mixture is stirred at room temperature for 1 h and then water (100 ml) is added to quench remaining acetyl imidazole.

d) *Purification*. The mixture from the acetylation is heated to 30-35°C and 1-butanol (4,5 L) is added to prevent precipitation The mixture is extracted twice at pH 5 (2 x 2,6 L water), and twice at pH 11 (2 x 2,6 L water) using NaOH to adjust pH to 11. Methanol (2,25 L) is added to the last extractions to prevent precipitation. NaCl (130 g) is added to the first and the last extraction to minimize loss of product in the aqueous phases.

e) *Isolation*. To the vigorously stirred organic phase from the extractions is added heptane (15 L) and the resulting suspension is left at room temperature while stirring for at least 1 h. The mixture is filtered and the product is washed twice with heptane (2 x 3,5 L) and dried. Yield: 75% (from Boc-D-4ClPhe-D-3Pal-OH). HPLC purity: 92%. Amino acid analysis: 2Nal: 1.1; 4ClPhe: 1.0; 3Pal: 0.9. MS: MW 586. Na: 4.6%

EXAMPLE 6. Ac-D-2Nal-D-4ClPhe-D-3Pal-OH·DCHA

a) *Deprotection*. To the solid Boc-D-2Nal-D-4ClPhe-D-3Pal-OH is added water (90 mL), acetic acid (1,8 L) and MSA (454 mL; 7,0 eq.) and the mixture is stirred for 1-2 h at room temperature. The mixture is cooled to 0°C and neutralized with TEA (1071 mL; 7,7 eq.). The solution is concentrated *in vacuo* and co-evaporated twice with toluene (2 x 2,5 L) to give an oil.

b) *Acetylation*. The oil from the deprotection is dissolved in toluene (2,0 L) and acetyl imidazole (132,14 g) is added. The mixture is stirred at room temperature for 1 h followed by addition of water (100 ml) to quench remaining acetyl imidazole.

c) *Purification*. The mixture is heated to 30-35°C and 1-butanol (4,5 L) is added to prevent precipitation. The mixture is extracted twice at pH 7 (2 x 2,6 L water), once at pH 9-9,5

(2,6 L water) and once at pH 7 (2,6 L water). DCHA (dicyclohexyl amine) is added and the mixture is concentrated *in vacuo*. The product is suspended in 1-butanol (4,5 L) at 50°C and slowly added to vigorously stirred heptane (27 L). The mixture is stirred at 0°C over night, filtered and the product washed twice with 1-butanol/heptane (1:3; 2x4,8 L) and twice with heptane (2x4,5 L). Yield: 65% (from Boc-D-4ClPhe-D-3Pal-OH). HPLC purity: 94,2%. Amino acid analysis: 2Nal: 1.1; 4ClPhe: 1.0; 3Pal: 0.9. MS: MW 586 (free peptide).

EXAMPLE 7. Ac-D-2Nal-D-4ClPhe-D-3Pal-OH.

a) Deprotection. To the solid Boc-D-2Nal-D-4ClPhe-D-3Pal-OH is added water (90 mL), acetic acid (1,8 L) and MSA (454 ml; 7,0 eq.) and the mixture is stirred for 1-2 h at room temperature. The mixture is cooled to 0°C and neutralized with TEA (1071 mL; 7,7 eq.). The solution is concentrated *in vacuo* and co-evaporated twice with toluene (2 x 2,5 L) to give an oil.

b) *Acetylation*. The oil from the deprotection is dissolved in toluene (2,0 L) and acetyl imidazole (132,14 g) is added. The mixture is stirred at room temperature for 1 h and then water (100 mL) is added to quench remaining acetyl imidazole.

c) Purification. The mixture from the acetylation is heated to 30-35°C and 1-butanol (4,5 L) is added to prevent precipitation The mixture is extracted twice at pH = 7 (2 x 2,6 L water), and once at pH = 9-9,5 (2,6 L water) and once at pH=7 (2,6 L water). The mixture is concentrated *in vacuo* to an oil, which is dissolved in acetic acid (750 ml), concentrated, re-dissolved in acetic acid (750 ml) and slowly added to vigorously stirred heptane/ethyl acetate (3:1; 3,6 L). The mixture is left with stirring at 0°C over night. The mixture is filtered, and the product is washed twice with ethyl acetate/ heptane (1:3; 2x3,6 L) and twice with heptane (2x3,6 L).

Yield: 70% (from Boc-D-4ClPhe-D-3Pal-OH). HPLC purity: 93,9%.
Amino acid analysis: Nal: 1.1; 4ClPhe: 1.0; 3Pal: 0.9
MS: MW 586 (free peptide).

CLAIMS

1. A process for preparing a tripeptide, including a salt thereof, of the formula (I)

Ac-D-2Nal-D-4ClPhe-D-3Pal-OH (I)

or (IX)

Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX),

comprising the following consecutive steps for the preparation of (I):

(a) Reacting Boc-D-4ClPhe-OH with HONSu to form Boc-D-4ClPhe-OSu (VII);

(b) Reacting Boc-D-4ClPhe-OSu (VII) with H-D-3Pal-OH to form Boc-D-4ClPhe-D-3Pal-OH (VIII);

(c) Reacting Boc-D-4ClPhe-D-3Pal-OH (VIII) with Boc-D-2Nal-OSu prepared by reacting Boc-D-2Nal-OH with HONSu to form Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX);

(d) Reacting Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX) with acetic acid to form Ac-D-2Nal-4ClPhe-D-3Pal-OH (I);

or the consecutive steps (a) through (c) for the preparation of (IX).

2. The tripeptide Ac-D-2Nal-D-4ClPhe-D-3Pal-OH (I) or a salt thereof.

3. The tripeptide Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX) or a salt thereof.

4. A process for preparing an LHRH antagonist or a pharmaceutically acceptable salt thereof, comprising coupling

a tripeptide Ac-D-2Nal-D-4ClPhe-D-3Pal-OH (I) with a heptapeptide (IV) of the general formula

P^1-Ser(P^2)-AA1-AA2-Leu-Lys(iPr,P^4)-Pro-D-AlaNH_2 (IV),

wherein P^1 is selected from H or amino protecting group, P^2 is H or OH-protecting group, P^4 is H or an amino protecting group such as Boc, AA1 is natural or synthetic amino acid and AA2 is natural or synthetic amino acid or zero.

5. The process of claim 4, wherein the heptapeptide of the general formula (IV) is a heptapeptide of the general formula

P^1-Ser(P^2)-NMeTyr(P^3)-D-Lys(Nic)-Leu-Lys(iPr,P^4)-Pro-D-AlaNH_2 (V)

wherein P^3 is H or -OH protecting group.

6. The process of claim 4, wherein the heptapeptide of the general formula (IV) is a heptapeptide of the general formula

P^1-Ser(P^2)-NMeTyr(P^3)-D-Asn-Leu-Lys(iPr,P^4)-Pro-D-AlaNH_2 (Va).

wherein P^3 is H or -OH protecting group.

7. The process of claim 5, wherein the heptapeptide of the general formula (V) is a heptapeptide of the formula

H-Ser(tBu)-NMeTyr-D-Lys(Nic)-Leu-Lys(iPr,Boc)-Pro-D-AlaNH_2 (VI).

8. The process of claim 6, wherein the heptapeptide of the formula (VI) is a heptapeptide of the formula

H-Ser(tBu)-NMeTyr-D-Asn-Leu-Lys(iPr,Boc)-Pro-D-AlaNH_2 (VIa).

9. A process for preparing an LHRH antagonist or a pharmaceutically acceptable salt thereof, comprising coupling the tripeptide Boc-D-2Nal-D-4ClPhe-D-3Pal-OH (IX)

with a heptapeptide (IV) of the general formula

P^1-Ser(P^2)-AA1-AA2-Leu-Lys(iPr,P^4)-Pro-D-AlaNH$_2$ (IV),

wherein P^1 is selected from H or amino protecting group, P^2 is H or OH-protecting group, P^4 is H or amino protecting group such as Boc, AA1 is a natural or synthetic amino acid and AA2 is a natural or synthetic amino acid or zero.

10. The process of claim 9, wherein the heptapeptide of the general formula (IV) is a heptapeptide (V) of the general formula

P^1-Ser(P^2)-NMeTyr(P^3)-D-Lys(Nic)-Leu-Lys(iPr,P^4)-Pro-D-AlaNH$_2$ (V)

wherein P^3 is H or OH-protecting group.

11. The process of claim 10, wherein the heptapeptide of the general formula (V) is the heptapeptide

H-Ser(tBu)-NMeTyr-D-Lys(Nic)-Leu-Lys(iPr,Boc)-Pro-D-AlaNH$_2$ (VI).

12. The process of claim 9, wherein the heptapeptide of the general formula (IV) is a heptapeptide of the general formula

P^1-Ser(P^2)-NMeTyr(P^3)-D-Asn-Leu-Lys(iPr,P^4)-Pro-D-AlaNH$_2$ (Va),

followed by substituting the Boc group by an acyl group, in particular an acetyl group.

13. The process of claim 12, wherein the heptapeptide of the general formula (IV) is the heptapeptide

H-Ser(tBu)-NMeTyr-D-Asn-Leu-Lys(iPr,Boc)-Pro-D-AlaNH_2 (VIa),

followed by substituting the N-terminal Boc group by an acyl group, in particular an acetyl group.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/[redacted]2/05583

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07K 5/083
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5710246 A (KENNETH W. FUNK ET AL), 20 January 1998 (20.01.98), see the claims and column 40, line 39	2-13

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2003	07 -04- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on pat[redacted]amily members

28/02/03

International application No.
PCT/I[redacted]2/05583

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5710246 A	20/01/98	EP 0889901 A,B	13/01/99
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